Sequentially Administered Ethinyl Estradiol and Medroxyprogesterone Acetate in the Treatment of Refractory Epithelial Ovarian Carcinoma in Patients With Positive Estrogen Receptors

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The activity of sequentially administered hormonal therapy was investigated over 25 days in 25 patients with epithelial ovarian carcinoma who had estrogen receptor (ERc)-positive tumors. Patients received ethinyl estradiol (EE) (50 μg/d) on days 1 to 7 and medroxyprogesterone acetate (MPA) (400 mg/d) on days 8 to 25. Twenty-three patients completed one or more courses of treatment. There were no complete responses (CR). Four partial responses (PR) with durations of 9, 4, 3, and 1 months were seen. Two incomplete responses with durations of 6 and 4 months were also seen. Six patients had stable disease (SD), and 11 patients had progression. The overall response rate was 17% and may represent a modest improvement in response over those in previously published studies conducted with MPA alone. No significant toxic effects were noticed, and some patients reported an improved sense of well-being. However, two patients experienced depression with this treatment. The mean ERc values in responders, patients with SD, and nonresponders were 70.0, 36.7, and 47.9 fmol/mg cytosolic protein, respectively. Future studies of hormonal therapy in patients with ovarian carcinoma should attempt to identify more reliable indices for determining sensitivity to these agents.
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DESPITE RECENT ADVANCES in the surgical and medical management of epithelial carcinoma of the ovary, this disease continues to be the major contributor to annual deaths from tumors arising in the female genital tract.[1] Chemotherapy-resistant cancers, such as epithelial ovarian cancer, are a significant management problem. Patients in whom cisplatin-containing regimens fail rarely respond to other agents.[2] Renal and neurologic effects and toxic effects due to myelosuppression become more of a consideration in older patients and in patients who have already received prolonged or repeated chemotherapy.

The search for alternative treatment modalities for ovarian cancer has included the use of hormonal agents, predicated on successes in the hormone-based treatments for malignancies arising from other hormone-dependent tissues (notably the breast and endometrium). The relatively low toxicity of hormonal therapy also makes such treatment an attractive prospect. Response rates to progestational agents in the treatments of patients with epithelial ovarian cancers have been reported from 0% to 49%,[5–14] although response criteria were frequently difficult to evaluate in these trials. More recent reports have defined eligibility and response criteria and have shown objective response rates of 14%.[5–7,9,12–14] However, several recent trials conducted with patients with ovarian cancer who were treated with medroxyprogesterone acetate

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(MPA) alone have showed a response rate of less than 5%.[5-7,12]

In an earlier trial at the University of Texas M. D. Anderson Cancer Center, Houston, Texas, using sequentially administered ethinyl estradiol (EE) and MPA, 14% of patients had a partial response (PR) and 20% had stable disease (SD).[15] Receptor data were available on only a small number of the study group. However, patients with higher estrogen receptor (ERc) and progesterone receptor (PRc) values did have PR or SD on treatment. Two responses were seen among eight patients whose ERc values were greater than or equal to 10 fmol/mg cytosolic protein, but no responses were seen among ten patients whose ERc values were less than 10 fmol/mg cytosolic protein.

In malignancies of the breast and endometrium, responses to progestational agents are higher in patients whose tumors are PRc positive.[16] Furthermore, exposure of ERc-positive tissues to estrogen is known to induce the production of PRc.[17,18] Yet, receptor data have been infrequently applied to hormonal therapy strategies in ovarian carcinoma. In one recent attempt to do so, Nash *et al.*[19] identified the endocrine characteristics of two ovarian cancer cell lines. In one line, estrogen treatment induced PRc production without cellular proliferation. Those authors speculated that a tumor with cells similar to those in that cell line could be treated with progestational agents after estrogen priming. Hortobagyi *et al.*[20] used the approach of estrogen priming followed by high-dose progesterone therapy in the management of patients with breast cancer and saw a 57% response rate.[20] Three patients in that study had sequential biopsies performed to evaluate hormone receptors and demonstrated a substantial decrease in ERc and a marked increase in PRc after 7 days of EE therapy. Toxicity of the hormones was minor.

Such recent research on the feasibility of alternative hormonal therapies for ovarian cancer has led us to the current study. Our study prospectively evaluated the activity and toxic effects of sequentially administered EE and MPA in patients with refractory or advanced epithelial ovarian tumors that have ERc values greater than or equal to 10 fmol/mg cytosolic protein.

Materials and Methods

Patients were eligible for entry into the trial if they had refractory or advanced epithelial carcinoma of the ovary, a life expectancy of at least 12 weeks, a performance status of less than or equal to 2 on the Zubrod scale, and were capable of eating without significant nausea or vomiting. Patients were also required to have measurable disease, and hormone receptor data on either primary or metastatic tumors with an ERc value greater than or equal to 10 fmol/mg cytosolic protein had to be available. PRc values were obtained whenever adequate tissue permitted. A PRc value of greater than or equal to 10 fmol/mg cytosolic protein was considered positive. ERc and PRc were measured in standardized assays performed in the laboratory of clinical chemistry at the M. D. Anderson Cancer Center.[21] Any patient with a history of pulmonary embolism, acute myocardial infarction, acute cerebrovascular thrombosis or embolism, or currently uncontrolled hypertension (diastolic blood pressure greater than or equal to 130 mmHg) was excluded. Previous deep venous thrombosis alone was not a basis for exclusion. Patients were also excluded if they had received any sex steroids in the month before their entry in the study. All patients signed an informed consent form.

Patients who met the criteria received EE orally (50 μg/d) on days 1 to 7 and MPA orally (400 mg/d) on days 8 to 25. No medication was administered on days 26 to 30, following which the cycle was repeated. This dosage of EE was identical to that used in an earlier trial, but the MPA dose was doubled.[15] Higher dosages of progestins have been associated with improved response rates in patients with carcinoma of the endometrium and breast.[9] A supply of 400-mg MPA tablets was provided by The Upjohn Company (Kalamazoo, MI). Patient compliance with the medication regimen was reviewed by the study research nurse (W. S.). Patients were monitored for response to therapy by physical examination and appropriate radiologic studies. Liver function and coagulation studies were conducted at 1-month to 3-month intervals.

Response criteria were based on World Health Organization recommendations.[22] Briefly, a complete response (CR) was defined as the complete disappearance of all clinically or radiologically documented lesions for at least 4 weeks. PR was defined as a 50% reduction in the sum of the product of the maximum perpendicular tumor diameters for a minimum of 4 weeks and the absence of progressive disease at other sites. SD was defined as no change in the tumor diameters for a minimum of 8 weeks. A minor response (MR) category was included in the study for tumors that were reduced by less than 50% in diameter; however, MR were not considered objective responses.

Statistics

For the purpose of this trial, therapy was considered unacceptable or not useful if the response rate was less than 20%. To ascertain this, patients were accrued in three groups of 12 patients each. In the first group of 12 patients, if one or no response was observed, then the trial was to be terminated and the treatment declared ineffective. If seven or more responses were observed, then the trial was to be terminated and the treatment declared effective. If two to six responses were observed, then a second cadre of 12 patients was to be added to the first. If in these 24

TABLE 1. Clinical Characteristics of Study Population

Variables	No. of patients
Stage	
I	1
II	3
III	13
IV	4
Unknown	2
Histologic condition	
Serous	14
Endometrioid	4
Other	5
Grade	
1	1
2	8
3	13
Unknown	1
Previous therapy	
Surgery	23
Radiation therapy	4
Cisplatin chemotherapy	23
≥ 2 lines of chemotherapy	13
≥ 4 lines of chemotherapy	3
Zubrod status	
0	7
1	9
2	7
Previous response to therapy	
Complete response	4
Partial response	5
Recurrent disease sites	
Pelvis	13*
Abdomen	4*
Pelvis and abdomen	5*
Supraclavicular node	1

* One patient with pleural effusion in each group.

patients, six or fewer responses were observed, then the trial was to be terminated and the treatment declared ineffective. If ten or more responses were observed, then the trial was to be terminated and the treatment declared effective. This design provided an 80% power for the alternative hypothesis that the response rate was 40% against the correct hypothesis that the response rate was 20%, when testing at the 5% significance level.

Results

Twenty-five eligible patients were enrolled in this trial. Two patients died less than 1 month after entry and were not included in analysis. Clinical characteristics of the 23 patients enrolled are shown in Table 1. The median age at the time of entry was 55 years of age (range, 29 to 69 years of age). Two-thirds of the patients had serous tumors, and only one of those tumors was well differentiated. All patients had previously received chemotherapy that included cisplatin. Site of disease at study entry was almost exclusively in the pelvis or abdomen or both. Twenty-three patients were evaluable for response and toxic reactions.

No CR were observed. PR were seen in 4 of 23 evaluable patients (17.4%), MR in 2 (8.7%), and SD in 6 (26%). Disease progression was seen in 11 patients. Table 2 provides clinical characteristics of patients with response or SD, Table 3 shows response by receptor value criteria, and Table 4 shows response by age. Responses appear to be more common among patients with higher ERc values. PRc data were available on only 11 patients, and the 2 patients with the highest values both had PR. Younger patients (50 years of age or younger) were more likely to show a response to therapy. The mean ages of responders, patients with SD, and nonresponders were 46.5, 53.2, and 55.7 years of age, respectively.

Toxicity

No Grade 3 or 4 toxicity was observed. No patient had deep venous thrombosis, cerebrovascular accident, or

TABLE 2. Patients With Response or Stable Disease

Age (yr)	Grade	Histologic condition	Previous therapy	Previous response	Disease site	Receptor data		No. of courses	Response	Duration response (mo)	Status	Survival (mo)
						ERc	PRc					
44	3	E	S, C, R	CR	SCLN	94.0	—	4	PR	1	D	30
45	3	SE	S, C, R	UNK	P	29.6	—	6	PR	4	AD	38+
53	3	SE	S, C	PD	A	37.9	97.1	7	PR	3	D	15
63	2	SE	S, C	PR	A, P	115.0	54.0*	13	PR	9	AD	13+
55	1	E	S, C	SD	P	18.1	—	6	MR	4	D	11
67	UNK	SE	S, C, R	SD	P	23.4	—*	11	MR	6	D	14
49	2	E	S, C	PR	A	13.0	3.1	5	SD	3	D	13
60	3	SE	S, C	PD	P	23.6	—	3	SD	2	D	14
28	3	SE	S, C	PD	P	43.1	—	21	SD	20	AD	35+
64	2	SE	S, C	PD	P	71.2	—	3	SD	2	D	5
48	3	SE	S, C	CR	A, P, PL	27.0	3.0	3	SD	2	D	3
44	3	UNK	S, C	UNK	A, P	34.0	—	3	SD	2	D	4

ERc: estrogen receptor value in fmol/mg cytosolic protein; PRc: progesterone receptor value in fmol/mg cytosolic protein; E: endometrioid; S: surgery; C: chemotherapy; R: radiation therapy; CR: complete response; SCLN: supraclavicular lymph node; PR: partial response; D: dead of disease; SE: serous; UNK: unknown; P: pelvis; AD: alive with disease; PD: progressive disease; A: abdomen; SD: stable disease; MR: minimal response; PL: pleural effusion.

* Receptor data on primary, not recurrent, cancer.

TABLE 3. Response by Receptor Value Criteria

Receptor values		No. of patients					
		CR	PR	MR	SD	P	Total
$10 \leq$ ERc < 30	$1 \leq$ PRc < 10	0	0	0	2	0	2
$10 \leq$ ERc < 30	$10 \leq$ PRc < 50	0	0	0	0	3	3
$10 \leq$ ERc < 30	PRc > 50	0	0	0	0	0	0
$10 \leq$ ERc < 30	PRc UNK	0	1	2	1	3	7
ERc ≥ 30	$1 \leq$ PRc < 10	0	0	0	0	0	0
ERc ≥ 30	$10 \leq$ PRc < 50	0	0	0	0	4	4
ERc ≥ 30	PRc > 50	0	2	0	0	0	2
ERc ≥ 30	PRc UNK	0	1	0	3	1	5
Total		0	4	2	6	11	23

CR: complete response; PR: partial response; MR: minimal response; SD: stable disease; P: progressive disease; ERc: estrogen receptor value in fmol/mg cytosolic protein; PRc: progesterone receptor value in fmol/mg cystosolic protein.

myocardial infarction. Blood pressure elevations occurred in two patients, one of whom required antihypertensive therapy. Two patients experienced mood elevation and euphoria, and two others experienced depression that appeared to be associated with the hormonal regimen. Results of liver function studies in six patients showed asymptomatic enzyme elevations. Four patients had mild elevations in either lactic dehydrogenase (LDH) or serum glutamic pyruvic transaminase (SGPT) levels, and two patients had moderate elevations in alkaline phosphatase, LDH, and SGPT levels. Results of coagulation studies showed no significant changes in antithrombin III (AT III) levels, but one patient had an abnormal elevation in her prothrombin (PT) level.

Discussion

In the current study, the sequential administration of EE and MPA to patients with refractory or advanced epithelial cancers of the ovary with tumor ERc values greater than or equal to 10 fmol/mg cytosolic protein produced objective responses in 17.4% of patients and MR or SD in 34.7%. This trial attempted to determine the relationship between responsiveness to sequentially administered EE and MPA and ERc tumor status. In patients whose tumors were ERc positive, an objective response rate of 17% was seen. Several of the patients had either MR or SD of several months duration that may have contributed to improvement in overall quality of life. The lower than expected response rate could be explained in part by the heterogeneity of receptor expression or inadequate knowledge of the critical ERc values required for tumor responsiveness to hormonal therapy.

TABLE 4. Response by Age

Age (yr)	No. of patients					
	CR	PR	MR	SD	PD	Total
≤ 50	0	2	0	2	2	4
> 50	0	2	2	4	9	19
Total	0	4	2	6	11	23

CR: complete response; PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease.

Before this report, there had been no systematic evaluation of hormonal therapy in ovarian cancer patients with ERc-positive tumors. Although our observed objective response rate of 17.4% is, at best, modest, it appears to indicate an improvement over previous trials in which MPA had been used alone. Other researchers have reported higher response rates with megestrol,[9,13,14] but these have not been confirmed.

Despite the results of this and other studies, the mechanism of action of hormonal therapy in reducing malignancy remains inadequately understood. Progestins may act by binding to cytoplasmic receptor proteins, with the interaction resulting in a decrease in chromatin, pleomorphism, and mitoses of susceptible tumors.[23] Estradiol has been shown to induce the production of PRc in ERc-positive human tumor xenografts,[17] and similar response has been seen in patients with ERc-positive tumors.[10] How this effect on receptor status ultimately leads to cell kill is unknown.

As more is learned of the relationship among cell response, receptor values, and hormonal therapy, we may be better able to discriminate patients who are best suited for hormonal treatment regimens. Recent data have suggested that hormonal receptor levels may not have a positive correlation to tumor response as a result of a defective binding or defective processing mechanism.[24] Nash *et al.*[19] have shown that cell growth and PRc induction do not occur together in estrogen-stimulated ERc-positive cells. These investigators have also shown *in vitro* that some tumor cell lines may be stimulated by estrogen, whereas others appear to be suppressed. Obviously, more sensitive and specific assays of biologic sensitivity to hormonal therapy are required.

Although objective response rates are modest, a substantial fraction of our patient population had SD or minimal response. Combining this feature with the low toxicity of this regimen makes sequentially administered EE and MPA an attractive alternative for patients with ERc-positive epithelial ovarian cancer in whom conventional cisplatin-based chemotherapy has failed. The treatment appears to offer some improvement over the administration of MPA alone, although comparisons with the use of other progestogens in hormonal approaches have not been made. Additional study may help define which patients are most likely to respond to hormone-based chemotherapy.

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